A TETRAHYDROCANNABINOL (Δ⁹ THC) SOLUTION METERED DOSE INHALERS AND METHODS OF USE

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Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

Appl. No.: 09/944,221
Filed: Sep. 4, 2001

Prior Publication Data

Related U.S. Application Data
Continuation-in-part of application No. 19/273,766, filed on Mar. 22, 1999, now Pat. No. 6,509,005
Provisional application No. 60/105,850, filed on Oct. 27, 1998.

Int. Cl. 7 .. A61L 9/04; A01N 43/16; A61K 31/35

U.S. Cl. ................. 424/45; 514/454

Field of Search .......... 424/43, 45, 46; 514/454

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4,635,651 A * 1/1987 Jacobs ................. 131/270
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ABSTRACT
The present invention provides therapeutic formulations for solutions of Δ⁹-tetrahydrocannabinol (Δ⁹ THC) to be delivered by metered dose inhalers. The formulations, which use, non-CFC propellants, provide a stable aerosol-deliverable source of Δ⁹ THC for the treatment of various medical conditions, such as nausea and vomiting associated with chemotherapy-muscle spasticity; pain; anorexia associated with AIDS wasting syndrome, epilepsy; glaucoma; bronchial asthma; and mood disorders.

16 Claims, 8 Drawing Sheets
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Delta–9–Tetrahydrocannabinol; Dept. of Psychiatry and Internal Medicine, University of Iowa College; Feb.–Mar. 1975; pp. 139–143.

Delta–9–Tetrahydrocannabinol and codine; Depart., of Psychiatry and Medicine, University of Iowa; published Mar. 29, 1975; pp. 84–89.

The effect of orally rectally administered 9–tetrahydrocannabinol on spasticity; A pilot study with 2 patients, Institute of Pharmacy, University of Bern; International Journal of Clinical Pharmacology and Therapeutics, vol. 34 No. 10–1966 (446–452).


Tetrahydrocannabinol for Tremor in Multiple Sclerosis; David Clifford, MD; Division of Clinical Neuropharmacology and Dept. fo Neurology and Neurological Surgery Washington School of Medicine; Published Dec. 12, 1982; Annals of Neurology vol. 13 No. 6 Jun. 1983; pp. 669–671.


Effect of Marihuana on Intracocular and Blood Pressure in Glaucoma; American Academy of Ophthalmology; Mar. 1980 vol. 87 No. 3; pp. 222–228.


Comparison of output particle Size Distributions from Pressurized Aerosols Formulated as Solutions or Suspensions; Pharmaceutical Research vol. 5 No. 1, 1988, Plenum Publishing Corp. pp. 36–39.


The Identification, isolation, and preservation of 9–tetrahydrocannabinol; Dept. of Toxicology, Indiana University Med. Ctr., J. Pharm. 1971, 23, 190–195.


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FIG. 1

FIG. 2
FIG. 5
HFA 134A

F

C

C

H

F

F

HFA 227

F

C

C

C

F

F

H

F

FIG. 6A

FIG. 6B
1. Field of the Invention

The invention is generally related to the therapeutic use of Δ⁹-Tetrahydrocannabinol (Δ⁹-THC). In particular, the invention provides a metered dose inhaler (MDI) for the aerosol administration of Δ⁹-THC to patients suffering from nausea and vomiting associated with cancer chemotherapy, muscle spasticity, pain, anorexia associated with AIDS wasting syndrome, epilepsy, glaucoma, bronchial asthma, mood disorders, and the like.

2. Background Description


<table>
<thead>
<tr>
<th>Condition and Number of Patients</th>
<th>Administration Route and Dose</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-associated anorexia and cachexia; 94 patients; 12 months</td>
<td>Oral placebo, 2.5 mg THC once or twice daily increasing to 20 mg daily</td>
<td>Long term THC treatment was well-tolerated; THC improved appetite and only tended to increase weight compared to controls 57% and 69% of vehicle and THC patients were evaluable for efficacy. Appetite increased 38% over baseline for THC group compared to only 8% for placebo.</td>
<td>Beal et al., 1997</td>
</tr>
<tr>
<td>AIDS-associated anorexia and cachexia; 139 patients; 42 days</td>
<td>Oral placebo or 2.5 mg THC twice daily</td>
<td></td>
<td>Beal et al., 1995</td>
</tr>
<tr>
<td>Condition and Number of Patients</td>
<td>Administration Route and Dose</td>
<td>Findings</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nausea and emesis due to Cancer chemotherapy; 84 patients</td>
<td>Oral placebo or 10 mg/m² THC every 3 hours for a total of 5 doses, THC (17 mg) laced cigarettes of placebo were given if vomiting occurred</td>
<td>93% patients had a reduction in nausea and vomiting, 55% had an excellent response, 40% had a fair response; plasma THC levels 7.1 ± 6.9 (mean ± SD) ng/ml. Side effects: tachycardia, few other side effects</td>
<td>Chang et al., 1979</td>
</tr>
<tr>
<td>Pain due to advanced cancer; 10 patients</td>
<td>Oral placebo and 5, 10, 15 or 20 mg THC</td>
<td>Pain relief, elevated mood, appetite stimulation, drowsiness, slurred speech, mental clouding</td>
<td>Noyes et al., 1975</td>
</tr>
<tr>
<td>Pain due to advanced cancer; 34 patients</td>
<td>Placebo, 10 and 20 mg THC, and 60 and 120 codeine</td>
<td>THC produced a similar degree of analgesia, with greater potency than codeine. THC CNS side effects included sedation, mental clouding, ataxia, and disorientation</td>
<td>Noyes et al., 1975</td>
</tr>
<tr>
<td>Spasticity related to multiple sclerosis; 2 patients</td>
<td>Oral 10 or 15 mg THC, rectal dose of 5 or 10 mg THC</td>
<td>Improvement in passive mobility and walking ability</td>
<td>Brenneisen et al., 1996</td>
</tr>
<tr>
<td>Spasticity related to multiple sclerosis; 13 patients</td>
<td>Oral 2.5 to 15 mg THC once or twice daily or placebo</td>
<td>Significant subjective improvement in spasticity at 7.5 mg THC and higher, no significant improvement in objective measurements</td>
<td>Ungeleider et al., 1987</td>
</tr>
<tr>
<td>Spasticity related to multiple sclerosis; 8 patients, single blind</td>
<td>Oral 5 to 15 mg THC</td>
<td>5 of 8 patients had mild subjective improvement in tremor. 2 of 8 patients had both subjective and objective improvement in spasticity.</td>
<td>Clifford, 1983</td>
</tr>
<tr>
<td>Spasticity related to multiple sclerosis; 9 patients</td>
<td>Placebo, or 5 or 10 mg THC</td>
<td>Decrease in spasticity compared to placebo treatment, minimal side effects</td>
<td>Petro and Ellenberger, 1981</td>
</tr>
<tr>
<td>Spasticity and pain due to spinal cord injury; 1 patient</td>
<td>Oral placebo, THC (5 mg), or codeine (50 mg)</td>
<td>THC and codeine had analgesic effect compared to the placebo treatment. THC had a beneficial effect on spasticity whereas codeine did not</td>
<td>Maurer et al., 1990</td>
</tr>
</tbody>
</table>

**TABLE 1-continued**

The Use of A THC for the Treatment of Assorted Clinical Conditions

<table>
<thead>
<tr>
<th>Condition and Number of Patients</th>
<th>Administration Route and Dose</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and emesis due to Cancer chemotherapy; 36 patients who had experienced severe nausea and vomiting that was refractory to prochlorperazine or thiethylperazine</td>
<td>Oral THC, 15 mg/m²</td>
<td>Reduction in chemotherapy-induced nausea and vomiting in 64% of patients given THC compared to prochlorperazine; side effects included drowsiness; authors recommend initial THC dose of 5 mg/m²</td>
<td>Lucas and Laszlo, 1980</td>
</tr>
<tr>
<td>Nausea and emesis due to Cancer chemotherapy; 116 patients</td>
<td>Oral 5 or 15 mg/m² THC four times per day</td>
<td>72% of patients exhibited a THC-induced partial or complete blockade of vomiting</td>
<td>Lucas and Laszlo, 1980</td>
</tr>
<tr>
<td>Nausea and emesis due to Cancer chemotherapy; 15 patients</td>
<td>Oral 10 mg/m² THC or placebo</td>
<td>THC more effective than prochlorperazine</td>
<td>Salmin et al., 1980</td>
</tr>
<tr>
<td>Nausea and emesis due to Cancer chemotherapy; 84 patients</td>
<td>Oral 5 or 15 mg THC, 10 mg prochlorperazine or placebo</td>
<td>Equal antiemetic effects between THC and prochlorperazine, effects of each greater than placebo; considerably more CNS side effects with THC than prochlorperazine</td>
<td>Frytak et al., 1979</td>
</tr>
<tr>
<td>Nausea and emesis due to Cancer chemotherapy; 15 patients</td>
<td>Oral placebo or 10 mg/m² THC every 3 hours for a total of 5 doses, THC (17 mg) laced cigarettes of placebo were given if vomiting occurred</td>
<td>8% for the placebo group. THC also decreased nausea. No significant changes were found between the groups for weight change.</td>
<td>McCabe et al., 1988</td>
</tr>
</tbody>
</table>

**Findings**

- Reduction in chemotherapy-induced nausea and vomiting in 64% of patients given THC compared to prochlorperazine.
- Side effects included drowsiness; authors recommend initial THC dose of 5 mg/m².
- 72% of patients exhibited a THC-induced partial or complete blockade of vomiting.
- THC more effective than prochlorperazine.
- Equal antiemetic effects between THC and prochlorperazine, effects of each greater than placebo; considerably more CNS side effects with THC than prochlorperazine.
- 8% for the placebo group. THC also decreased nausea. No significant changes were found between the groups for weight change.
### TABLE 1-continued

<table>
<thead>
<tr>
<th>Condition and Number of Patients</th>
<th>Administration Route and Dose</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma, 6 patients</td>
<td>Oral placebo or 5, 10, 15 and 20 mg THC</td>
<td>Pain relief, elevated mood, appetite stimulation, drowsiness, slurred speech, mental clouding</td>
<td>Merritt et al., 1980</td>
</tr>
<tr>
<td>Ten subjects with normal intra ocular pressure</td>
<td>Intravenous THC (0.022 or 0.044 mg/kg)</td>
<td>Decreased intra ocular pressure by mean of 37%</td>
<td>Cooler and Gregg, 1977</td>
</tr>
<tr>
<td>Nausea and emesis due to cancer chemotherapy; refractory to other antiemetics</td>
<td>Oral 10 mg/m² THC or placebo</td>
<td>In 20 courses of THC, 5 resulted in no vomiting, 9 resulted in a reduction of vomiting, 3 resulted in no decrease in vomiting, and 2 were unevaluable. THC was significantly better than placebo in decreasing vomiting</td>
<td>Sinn et al., 1975</td>
</tr>
</tbody>
</table>

The year after the 1997 NIH study, the House of Lords made a recommendation to the British government (House-of-Lords-Select-Committee-on-Science-and-Technology, 1998) to reschedule marijuana. Similarly, there have been efforts to decriminalize marijuana in the United States.

When marijuana is used as a recreational psychoactive drug, the active ingredient Δ⁸-THC is usually delivered to the lungs as an impure non-pharmaceutical aerosol in the form of marijuana smoke. Aerosolized Δ⁸ THC in the inhaled smoke is absorbed within seconds and delivered to the brain efficiently. The pharmacokinetics of the administration of Δ⁸ THC is described in PDR Physician’s Desk Reference (49) Montvale, New Jersey: Medical Economics Data Production Co. (1995), pp. 2787; Ohlsson, A., Lindgren J. E., Wahlen, A., Agurall, S., Hollister, L. E. and Gillespie, H. K., Plasma Δ⁸ THC concentrations and effects after oral and intravenous administration and smoking, *Clin Pharmacol Ther.* 28:409–416 (1980), summarized in Table 2 below. As can be seen, inhalation is the preferred route of delivery for Δ⁸ THC. When compared to oral delivery, inhalation provides a more rapid onset of pharmacological action and peak plasma levels. The effects achieved via inhalation are comparable to those achieved when the drug is administered intravenously, but inhalation is a much less invasive technique.

### TABLE 2

<table>
<thead>
<tr>
<th>Route, sesame oil in gelatin capsules</th>
<th>Dose</th>
<th>% Dose in Plasma</th>
<th>Onset of Pharmacological Action</th>
<th>Peak Plasma Levels</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral in gelatin capsules</td>
<td>2.5, 5, or 10 mg</td>
<td>10 to 20%</td>
<td>0.5 to 1 hour</td>
<td>120–480 min (PDR, 1995)</td>
<td></td>
</tr>
<tr>
<td>Oral in cookies</td>
<td>20 mg</td>
<td>4 to 12%</td>
<td>120–180 min</td>
<td>60–90 min</td>
<td>Ohlsson, et al., 1980</td>
</tr>
<tr>
<td>Intravenous bolus</td>
<td>5 mg</td>
<td>100%</td>
<td>10 min</td>
<td>3 min</td>
<td>Ohlsson, et al., 1980</td>
</tr>
<tr>
<td>Smoking (THC lost to side stream smoke and pyrolysis)</td>
<td>13 mg</td>
<td>8 to 24%</td>
<td>10 min</td>
<td>3 min</td>
<td>Ohlsson, et al., 1980</td>
</tr>
</tbody>
</table>

Currently, the sources of Δ⁸ THC for patients who could benefit from the drug are limited. An oral form of Δ⁸ THC (MARINOL) is marketed as a treatment for nausea and vomiting related to cancer chemotherapy, and as an appetite stimulant in patients suffering from AIDS wasting syndrome. In MARINOL, pharmaceutical grade Δ⁸ THC is dissolved in sesame oil, encapsulated in gelatin capsules and delivered orally. However, when the drug is taken orally, the absorption is slower and more variable than when inhaled, with an onset of action between 30 minutes and 2 hours (Table 2). Drawbacks of MARINOL include its slow onset of action and extensive first-pass metabolism (Matts, R. D., Shaw, L. M., Edling-Ovens, J., Engelman, K., Elsolyh, M. A., Bypassing the first-pass effect for the therapeutic use of cannabinoids, *Pharmacol Biochem Behav*, 44:745–747 (1993); Ohlsson, Lindgren, Whalen, Agurell, Hollister, Gillespie, Plasma delta-9-hydrocannabinol concentration and clinical effects after oral and intravenous administration and smoking, *Clin Pharmacol Ther.* (1980), supra; PDR, 2000; Perlin, E., Smith, C. G., Nichols, A. I., Almirez, R., Flora, K. P., Crabock, J. C., Peck, C.C., Disposition and bioavailability of various formulations of tetrahydrocannabinol in the rhesus monkey, *J Pharm Sci*, 74:171–174 (1985)). There is also the difficulty of taking an oral medication during nausea and vomiting.

In contrast, inhalation of marijuana smoke (as some cancer patients do to alleviate nausea and vomiting due to... |

The Institute of Medicine (IOM) recently reviewed the scientific evidence for the potential of marijuana and its cannabinoid constituents to act as therapeutic agents. Joy, J., Watson Jr., S., Benson, J. E., Marijuana and Medicine: Assessing the Science Base (Washington, D.C.: National Academy Press, 1999). This report concluded that there is a potential for cannabinoid drugs, mainly Δ⁹ THC, for alleviation of pain, control of nausea and vomiting, and stimulation of appetite. However, they pointed out that marijuana is a “crude Δ⁹—THC delivery system” that delivers harmful chemicals along with the delivery of Δ⁹ THC, and recommended instead the development of a rapid-onset, reliable, and safe delivery Δ⁹ THC system. The House of Lords Select Committee on Science and Technology (Ninth Report) made similar suggestions to the British Government (House-of-Lords-Select-Committee-on-Science-and-Technology, 1998). Although the scheduling of cannabis has not been changed by the British or U.S. governments, the U.S. FDA has rescheduled MARINOL to a Schedule 3 drug, thus increasing the feasibility of developing other delivery forms of the drug.

There is no currently available pharmaceutically acceptable aerosol form of Δ⁹ THC. It would be advantageous to have a form of pharmaceutical grade Δ⁹ THC that could be administered as an aerosol. This would provide a means for rapid uptake of the drug. Also, the potential adverse side effects encountered by smoking marijuana would be avoided. Further, an aerosol preparation of pharmaceutically pure Δ⁹ THC could be administered in known, controlled dosages. Olsen et al. described a chlo-rofluorocarbon (CFC) propelled MDI formulation of Δ⁹ THC. Olsen, J. L., Lodge, J. W., Shapiro, B. J. and Taskin, D. P. An inhalation aerosol of Δ⁹-tetrahydrocannabinol, *J Pharmacy and Pharmacol.*, 28:86 (1976). However, Δ⁹ THC is known to deteriorate during storage, and the stability of Δ⁹ THC in this formulation is suspect. In addition, the ethanol content in this formulation was so high (~23%) as to create an aerosol with droplets too large to be effectively inhaled. Dabny, R. N. and Byron, P. R., Comparison of output particle size distributions from pressurized aerosols formulated as solutions or suspensions, *Pharm. Res.*, 5:36–39 (1988). The Δ⁹ THC CFC formulations were tested for use in treating asthma but were shown to be only moderately effective. Taskin, D. P., Reiss, S., Shapiro, B. J., Calvarose, B., Olsen, J. L. and Lidige, J. W., Bronchial effects of aerosolized Δ⁹-tetrahydrocannabinol in healthy and asthmatic subjects, *Amer Rev of Resp Disease*, 115:57–65 (1977); Williams, S. J., Hartley, J. P. R. and Graham, J. D. P., Bronchodilator effect of delta-9-THC administered by aerosol to asthmatic patients. *Thorax*, 31:720–723 (1976). Moreover, CFC propellants have since been banned so that a CFC propellant alternative would be particularly useful. It would clearly be advantageous to develop new aerosol formulations using a non-CFC propellant and having other advantageous features.

To date, much of the Δ⁹-THC aerosol exposure in humans concentrations on the bronchodilator effects of Δ⁹-THC. Taskin et al. (1977) used a Δ⁹-THC MDI to deliver aerosolized Δ⁹-THC to healthy and asthmatic patients in an effort to assess bronchodilatation as well as possible side effects due to systemic absorption. Taskin, D. P., Reiss, S., Shapiro, B. J., Calvarose, B., Olsen, J. L., Lodge, J. W., Bronchial effects of aerosolized delta-9-tetrahydrocannabinol in healthy and asthmatic subjects, *Am Rev Respir Dis*, 115:57–65 (1977). In healthy patients, bronchodilatation was seen, as well as substantial systemic side effects (increased heart rate and subjective reports of being ‘high’) at higher doses. However, in some asthmatic patients, bronchoconstriction occurred. Taskin et al. suggested that large particle size of the Δ⁹-THC aerosol may have caused the local irritant effects. Vachon et al. (1976) reported the use of a nebulized Δ⁹-THC micro-aerosol to achieve bronchodilatation without systemic effects, however, the propylene glycol vehicle had irritant effects. Vachon, J., Robins, A., Gaensler, E. A., Airways, response to aero-
solized delta-9-tetrahydrocannabinol: preliminary report, in The therapeutic potential of marijuana, eds. Cohen, S., Stillman, R.C., pp. 111–121 (New York: Plenum Medical Book Co., 1976). Williams et al. (1976) also used a low concentration of Δ⁹-THC for bronchodilation without systemic side effects or detectable levels of Δ⁸-THC in the blood. Williams, S. J., Hartley, J. P., Graham, J. D., Bronchodilator effect of delta-9-tetrahydrocannabinol administered by aerosol of asthmatic patients, Thorax, 6:720–723 (1976). It would clearly be advantageous to develop new aerosol formulations in which the Δ⁹-THC is stable, the droplets are of a size that can be effectively inhaled, and which use a non-CFC propellant.

Such objectives have been long desired but difficult to achieve, because of problems such as the difficulty of working with Δ⁹-THC, large dosage amounts required for Δ⁹-THC, and properties of Δ⁹-THC that make it unlike, and not interchangeable with, most other drugs. For example, Δ⁹-THC resembles rubber-cement, rather than a powder like most drugs, and thus presents formulation difficulties. Scientists working with THC found that they had to go to great lengths to combat its instability, based on its instability to light, oxygen, acids, bases, metal ions, etc. Thus, after the initial interest in the 1970s in THC/CFC aerosols, scientists generally settled into an acceptance of the unworkability of a THC aerosol. The initial promise of a THC aerosol according to J. L. Olsen, J. W. Lodge, B. J. Shapiro and D. P. Tashkin (1975) never materialized, and in the past few decades it has been conventionally thought that THC is not suited for aerosol-dispensing, and especially not for MDI-dispensing.

Thus, a pharmaceutically effective THC aerosol that overcomes the above-mentioned limitations of the prior art, especially an MDI-dispensable aerosol would be much desired.

**SUMMARY OF THE INVENTION**

The present inventors have now discovered, surprisingly, that THC dissolves well in HFA and that an aerosol-dispensable THC/HFA, pharmaceutical composition—i.e., a sufficiently stable composition and at the high doses which are required for THC—may be formulated. The present invention exploits these surprising discoveries. It is an object of the present invention to provide a stable aerosol-dispensable pharmaceutical composition comprising a non-CFC propellant and a pharmaceutically effective concentration of Δ⁹-THC, and Δ⁹ THC derivatives (e.g., cannabinoids such as Δ⁹-tetrahydrocannabinol, 11-hydroxy Δ⁹-tetrahydrocannabinol, cannabihexol, nabilone, levonantradol, (--)HU-210, Win 55212-2, Anandamide, Methanadamide, CP 55940, O-1057, SR141716A, etc.). More particularly, it is an object of the present invention to provide a stable aerosol-dispensable pharmaceutical composition comprising a hydrofluoroalkane propellant (for example, HFA 227 or HFA 134a) and Δ⁹-THC. The propellant is present in the range of approximately 78 to 100% by weight, and more particularly the propellant is present in the range of approximately 85 to 100% by weight. An organic solvent such as ethanol can be used to assist in solubilizing the Δ⁹-THC in the propellant but is not required. If a solvent is used, preferably less than 20% by weight will be required, and most preferably less than 15% by weight will be required. The pharmaceutically effective concentration of Δ⁹-THC is preferably in the range of 0.05 to 10% by weight, and most preferably in the range of 0.1 to 6% by weight. The pharmaceutical composition of the present invention can be used to treat a variety of medical conditions including nausea and vomiting associated with cancer chemotherapy, muscle spasticity, pain, anorexia associated with AIDS wasting syndrome, anorexia associated with cancer chemotherapy, epilepsy, glaucoma, bronchial asthma, mood disorders, migraine headaches.

**DETAILED DESCRIPTION OF THE INVENTION**

The instant invention provides non-ozone depleting pressurized metered dose inhaler formulations of Δ⁹-THC. In preferred embodiments of the invention, the formulations contain the pharmaceutically acceptable, non-ozone depleting hydrofluoroalkane propellants HFA 134a (1,1,2,2-tetrafluoroethane) and HFA 227 (1,1,1,2,3,3,3-heptafluoropropane), or a mixture thereof.

When the propellant is a hydrofluoroalkane, it has been discovered that the propellant may be used with or without a solvent such as ethanol. Higher percentages of solvent generally allow higher levels of dissolution of Δ⁹ THC. However, higher percentages of solvent also cause droplet size to increase. In preferred embodiments of the invention, the range of propellant compositions, as shown in Table 3, may be from 100% propellant and 0% solvent to 85% propellant and 15% solvent. Within this range of from 100 to 80% propellant and from 0 to 20% solvent. It is expected that a wide variety of solvents, such as ethanol, propanol, propylene...
glycol, glycerol, polyethylene glycol, etc. may be used in the preparation of formulations contemplated by this invention.

Those skilled in the art also will recognize that the “respirable dose” (or mass of Δ⁰ THC in particles with aerodynamic diameters small enough to be delivered to and absorbed by the lungs) (FIG. 1) may be increased by choosing MDI spray nozzles of different design and smaller orifice diameters. Respirable doses may also be increased by extending the mouthpiece of the MDI in such a way as to create an integral or separate aerosol spacer or reservoir attached to the mouthpiece of the MDI. This promotes an increase in droplet evaporation and hence in the percentage of the dose in smaller “respirable” particles or droplets. Generally, the optimal size of a respirable droplet is less than 10 micrometers (μm) in size. The size of a droplet in an aerosol may be measured by cascade impaction and is characterized by the mass median aerodynamic diameter (MMAD) (the value for which 50% of the particles are larger or smaller). Using THC aerosols according to the present invention, an MMAD of 2.5 μm or better may be provided.

TABLE 3

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mass (g) of Δ⁰ THC in Sampled</th>
<th>Mass (g) of Formulation</th>
<th>Apparent Solubility</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ⁰ THC 100% HFA 134a</td>
<td>0.000240</td>
<td>0.1071</td>
<td>0.224% w/w (±0.063)</td>
<td>Excess Δ⁰ THC added to propellant blend (in pressurized MDI). Solubility sample removed using puff absorber. n = 5</td>
</tr>
<tr>
<td>Δ⁰ THC 5% ethanol/95% HFA 134a</td>
<td>0.00144</td>
<td>0.0914</td>
<td>1.585% w/w (±0.321)</td>
<td>As above</td>
</tr>
<tr>
<td>Δ⁰ THC 10% ethanol/95% HFA 134a</td>
<td>0.00363</td>
<td>0.1036</td>
<td>3.511% w/w (±0.249)</td>
<td>As above</td>
</tr>
<tr>
<td>Δ⁰ THC 15% ethanol/85% HFA 134a</td>
<td>0.00536</td>
<td>0.1098</td>
<td>4.883% w/w (±0.224)</td>
<td>As above</td>
</tr>
<tr>
<td>Δ⁰ THC 100% HFA 227</td>
<td>0.00021</td>
<td>0.1451</td>
<td>0.147% w/w (±0.008)</td>
<td>As above</td>
</tr>
<tr>
<td>Δ⁰ THC 5% ethanol/95% HFA 227</td>
<td>0.00134</td>
<td>0.0970</td>
<td>1.339% w/w (±0.169)</td>
<td>As above</td>
</tr>
<tr>
<td>Δ⁰ THC 10% ethanol/95% HFA 227</td>
<td>0.00454</td>
<td>0.1267</td>
<td>3.240% w/w (±0.161)</td>
<td>As above</td>
</tr>
<tr>
<td>Δ⁰ THC 15% ethanol/85% HFA 227</td>
<td>0.00623</td>
<td>0.1062</td>
<td>5.040% w/w (±0.191)</td>
<td>As above</td>
</tr>
</tbody>
</table>

A distinct advantage of the present formulations is that, surprisingly, the use of surface active agents or “surfactants” as valve lubricants and solubilizers is not necessary. This is in contrast to the invention of Purewal and Greenleaf (European Patent 0,372,777 (Riker Laboratories), Medicinal aerosol formulations) which provides HFA 134a/ethanol mixtures to produce stable formulations of pharmaceuticals in the presence of liposoluble active agents. Lipophilic surface active agents are incorporated in that invention in order to suspend undissolved material and to ensure adequate valve lubrication of the MDI. Without adequate valve lubrication, the useful life of the MDI and its ability to deliver an accurate dose of drug are severely attenuated. However, probably due to the inherent lubricity of the formulations of the present invention, the use of such surface active agents is unnecessary. This simplifies the composition and thus is an advantage with respect to cost and the elimination of potentially deleterious interactions between components of the formulations and the agents.

A major consideration in the formulation of any drug is its stability. Δ⁰ THC is known to deteriorate upon storage so that the effective concentration decreases and the purity is vitiated. The stability of the formulations of the present invention were tested according to accelerated storage testing protocols. The results are given in FIG. 1 and Tables 4A and 4B. The formulations of the present invention were shown to be stable with respect to the release of aerosolized Δ⁰ THC in reconstituted doses following accelerated storage testing. Apparently, the containment of Δ⁰ THC in solution in the non-aqueous formulations of the present invention is excellent with respect to chemical degradation, making possible the construction of a multidose inhaler with a good shelf life prognosis.
surprising preference of Δ9 THC for the formulation itself; rather than for the valve elastomers.

### TABLE 4A

Formulation and aerosol characteristics of Δ9 THC pressurized metered dose inhalers in ethanol/hydrofluoroalkane (HFA) propellant blends.

<table>
<thead>
<tr>
<th>Inhaler</th>
<th>Δ9 THC</th>
<th>Ethanol</th>
<th>Propellant Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.13%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Pale Yellow Solution</td>
</tr>
<tr>
<td>2</td>
<td>0.13%</td>
<td>~5%</td>
<td>95% HFA 227 3/98 Pale Yellow Solution</td>
</tr>
<tr>
<td>3</td>
<td>0.12%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Pale Yellow Solution</td>
</tr>
<tr>
<td>4</td>
<td>0.18%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Pale Yellow Solution</td>
</tr>
<tr>
<td>5</td>
<td>0.27%</td>
<td>~5%</td>
<td>95% HFA 227 3/98 Pale Yellow Solution</td>
</tr>
<tr>
<td>6</td>
<td>0.25%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Pale Yellow Solution</td>
</tr>
<tr>
<td>7</td>
<td>0.57%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Yellow Solution</td>
</tr>
<tr>
<td>8</td>
<td>0.58%</td>
<td>~5%</td>
<td>95% HFA 227 3/98 Yellow Solution</td>
</tr>
<tr>
<td>9</td>
<td>0.59%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Yellow Solution</td>
</tr>
<tr>
<td>10</td>
<td>1.02%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Yellow Solution</td>
</tr>
<tr>
<td>11</td>
<td>1.13%</td>
<td>~5%</td>
<td>95% HFA 227 3/98 Yellow Solution</td>
</tr>
<tr>
<td>12</td>
<td>0.97%</td>
<td>~5%</td>
<td>95% HFA 134a 3/98 Yellow Solution</td>
</tr>
<tr>
<td>SS** #1 Initial</td>
<td>1.07%</td>
<td>4.94%</td>
<td>94.0% HFA 134a 6/98 Yellow Solution</td>
</tr>
<tr>
<td>SS** #1 after 26 days at 40° C/82% RH</td>
<td>1.00%</td>
<td>5.01%</td>
<td>94.0% HFA 134a 7/98 Yellow Solution</td>
</tr>
<tr>
<td>SS** #2 after 21 days at 40° C/82% RH*</td>
<td>1.00%</td>
<td>5.01%</td>
<td>94.0% HFA 134a 7/98 Yellow Solution</td>
</tr>
<tr>
<td>SS** #3 Modified Actuator***</td>
<td>1.02%</td>
<td>5.15%</td>
<td>93.8% HFA 134a 10/98 Yellow Solution</td>
</tr>
</tbody>
</table>

*Mean (Standard Deviation) of five determinations.
**Mass of Δ9 THC aerosol particles < 5.8 μm aerodynamic diameter
***SS: Stability Sample
****RH: relative humidity
*****Approximate spray nozzle diameter = 0.2 mm.

### TABLE 4B

Formulation and aerosol characteristics of Δ9 THC pressurized metered dose inhalers in ethanol/hydrofluoroalkane (HFA) propellant blends.

<table>
<thead>
<tr>
<th>Aerosol Characterization</th>
<th>Inhailer</th>
<th>Metered Dose (mg)</th>
<th>Emitted Dose (mg)</th>
<th>Fine Particle Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1.72 (0.25)</td>
<td>1.32 (0.17)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.94 (0.23)</td>
<td>0.97 (0.10)</td>
<td>0.38 (0.02)</td>
<td></td>
</tr>
<tr>
<td>SS** #1 Initial</td>
<td>1.10 (0.07)</td>
<td>0.90 (0.03)</td>
<td>0.22 (0.03)</td>
<td></td>
</tr>
<tr>
<td>SS** #1 after 28 days at 40° C/82% RH**</td>
<td>1.06 (0.03)</td>
<td>0.92 (0.04)</td>
<td>0.23 (0.02)</td>
<td></td>
</tr>
<tr>
<td>SS** #2 after 21 days at 40° C/82% RH**</td>
<td>1.02 (0.05)</td>
<td>0.90 (0.05)</td>
<td>0.21 (0.02)</td>
<td></td>
</tr>
<tr>
<td>SS #3 Modified Actuator***</td>
<td>ND</td>
<td>ND</td>
<td>0.40 (n = 1)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean (Standard Deviation) of five determinations.
**Mass of Δ9 THC aerosol particles < 5.8 μm aerodynamic diameter
***SS: Stability Sample
****RH: relative humidity
*****Approximate spray nozzle diameter = 0.2 mm
ND: not determined.

The final concentration of Δ9 THC in a given formulation may be varied by adjusting the ratio of propellant to solvent and thus the solubility of the Δ9 THC. Higher percentages of solvent (e.g., ethanol) generally allow a higher amount of Δ9 THC to be dissolved. For example, in preferred embodiments of the invention, the apparent solubility of Δ9 THC and 15% ethanol. Thus, the dose of Δ9 THC in a given metered volume may be selected by changing the formulation.

Further, as stated above, the “fine particle dose” or “respirable dose” of a drug dispensed with an MDI is a function of the spray nozzle diameter. In FIG. 1 and Tables 4A and 4B, the spray nozzle diameter is 0.4 mm. The “fine particle dose” or “respirable dose” of the formulations of the present invention was shown to be unaffected by storage.

The Δ9 THC of the present invention is pharmaceutically pure. That is, its form is the nonionized resinous drug substance (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-penty1-6H-dibenzo[b,d]-pyran-1-ol. Although its preferred embodiment in this invention is not a salt or ester, it will be readily understood by those of skill in the art that other appropriate forms of Δ9 THC may be synthesized (e.g., esters and salts such as those described in, for example, U.S. Pat. No. 5,847,128 and PCT WO 01/03690, hereby incorporated in their entirety by reference) and thus used in the practice of this invention.

The desired final concentration of Δ9 THC in a patient’s serum will vary from patient to patient depending on, for example, the nature and severity of the condition being treated, and the patient’s overall condition, weight, gender and response to the drug, etc. But the desired range will generally be 10–100 ng/ml at 15 minutes following inhalation. The level of Δ9 THC in a patient’s serum can be readily and reliably monitored by gas chromatography/mass spectrometry (GC/MS).

The exact treatment protocol to be used may vary from patient to patient depending on the circumstances. For
example, in a preferred embodiment of the invention, a patient receiving chemotherapy may have one dose of $\Delta^8$-THC prescribed via inhalation, to be administered 15 minutes before chemotherapy and 4–8 times daily following chemotherapy. In another preferred embodiment, a patient suffering from anorexia associated with AIDS wasting syndrome may have $\Delta^8$-THC by inhalation prescribed 3–5 times daily, 30 minutes before each meal or snack. In other preferred embodiments, a patient suffering form cancer pain, or spasticity related to either multiple sclerosis or spinal cord injury may have $\Delta^8$-THC by inhalation prescribed 3–6 times daily. Those skilled in the art will readily recognize that the treatment protocol may be crafted so as to address the particular needs of each individual patient on a case by case basis.

$\Delta^8$-THC may be used alone or in combination with other medications. Those skilled in the art will readily recognize that, for example, in the case of AIDS wasting syndrome, the patient will likely also be taking drugs that combat the AIDS virus. Similarly, those skilled in the art will readily recognize that patients receiving chemotherapy for cancer may also receive other antiemetics, and cancer patients seeking to relieve pain are likely to receive opioids as well as nonsteroidal anti-inflammatory agents. The containers for the formulations of the instant invention may be any that are suitable for the efficacious delivery of aerosol inhalants. Several containers and their method of usage are known to those of skill in the art. For example, MDIs can be used with various dose metering chambers, various plastic actuators and mouthpieces, and various aerosol holding chambers (e.g. spacer and reservoir devices), so that appropriate doses of $\Delta^8$-THC reach and deposit in the lung and are thereafter absorbed into the bloodstream. In addition, a lock mechanism such as that shown in U.S. Pat. No. 5,284,133 to Bums and Marshak, which is herein incorporated by reference, can be used to prevent overdose or unauthorized consumption of $\Delta^8$-THC. FIG. 2 provides a generalized drawing of an MDI containing the composition of this invention and provides the advantage of delivering metered quantities of $\Delta^8$-THC on a repetitive basis. The MDI includes a container 100 for holding the composition and a valve delivery mechanism 102 for delivery of aerosolized $\Delta^8$-THC.

**IN VIVO EXPERIMENTATION**

A $\Delta^8$-THC MDI was formulated and the physical properties of the aerosolized drug characterized. The mass of drug metered by the metering valve was determined following a single actuation (metered dose). The mass of drug delivered (emitted dose) was determined. The mass of particles with an aerodynamic diameter less than 4.7 $\mu$m was determined.

Whether inhalation exposure to $\Delta^8$-THC aerosol would elicit pharmacological effects indicative of cannabinoid activity in mice (Compton, D. R., Rice, K. C., De Costa, B. R., Rzdan, R. K., Melvin, L. S., Johnson, M. R., Martin, B. R., Cannabinoid structure-activity relationships: Correlation of receptor binding and in vivo activities, *J Pharmacol Exp Ther*, 265:218–226 (1993); Little et al., 1988) was determined. To assess whether these effects were mediated through a cannabinoid receptor mechanism of action, the specific CB1, cannabinoid receptor antagonist SR 141716A (Rinaldi-Carmona et al., 1994) was used. Blood and brain levels of $\Delta^8$-THC were quantified to provide direct evidence that the drug was absorbed following inhalation exposure. The resulting blood and brain $\Delta^8$-THC concentrations following inhalation exposure were compared to those found following intravenous $\Delta^8$-THC administration using doses of drug that elicited similar antinociceptive effects.

Male ICR mice, weighing approximately 30 g, obtained from Harlan Laboratories (Indianapolis, Ind.) were provided a light cycle of approximately 6 a.m. to 6 p.m., and the temperature remained approximately 23°C. The mice were placed in the lab and allowed to accommodate to the surroundings the evening prior to testing. Animals were allowed food (Harlan Teklab, Madison, Wis.) and water ad libitum.

SR 141716A and $\Delta^8$-THC were obtained from the National Institute on Drug Abuse (Bethesda, Md.). For systemic injections, SR 141716A and $\Delta^8$-THC were dissolved in vehicle, 1:1:18 (ethanol:alkanum ESL-620 (formerly Emulphor EL-620, Rhone-Poulenc)saline). Each MDI consisted of a clean, dry, 20 ml plastic coated glass bottle (Wheaton Glass, Millville, N.J.) with a 100 ml inverted metering valve (BK 357, Bespak, Inc., Cary, N.C.). The MDI vehicle consisted of hydrofluoroalkane (HFA) 134a (DuPont, Wilmington, Del.) and ethanol (Aaper Alcohol and Chemical Co., Shelbyville, Ky.). The $\Delta^8$-THC MDIs were prepared using the methods of Byron, 1994 with a formulation that provided a theoretical ex-valve dose of 1 mg $\Delta^8$-THC per 100 ml actuation. Byron, P. R., Dosing reproducibility from experimental albuterol suspension metered-dose inhalers, *Pharm Res*, 11, 580–4 (1994).

Appearance, metered dose reproducibility, emitted dose and particle size distribution of the $\Delta^8$-THC MDI were investigated, before and after storage in an environment maintained at 40°C and 82% relative humidity for a 28 day period. The mass of drug metered by the metering valve (metered dose, n=10) was determined by collecting single actuations directly from the valve in a puff absorber, using the methods of Byron, 1994. The mass of drug delivered (emitted dose, n=10) was investigated at 28.31 min−1 using the USP Dosage Sampling Apparatus (USP, Physical Tests and Determinations, <601>), Aerosols, metered-dose inhalers, and dry powder inhalers, in *United States Pharmacopeia*, (USP 24), pp. 1895–1912 (Philadelphia, VA: National Publishing, 2000). Particle size analysis of $\Delta^8$-THC MDI was determined by drawing the samples through an Andersen Cascade Impactor (Andersen Samplers Inc., Atlanta, Ga.) at a volumetric flow rate of 28.3 liter/minute following United States Pharmacopeial guidelines (n=5; USP, 2000). The fine particle dose (n=5), defined as the mass of particles with an aerodynamic diameter less than 4.7 $\mu$m, was then determined.

THC was analyzed by LC-UV detection at 280 nm using a 75:25 acetonitrile: 1% acetic acid mobile phase for $\Delta^4$-THC detection. A standard reverse phase C18 column was used. A calibration curve was constructed for each assay based on linear regression of the $\Delta^2$-THC standard peak areas.

The exposure chamber was a modified, inverted, 1-liter separation funnel, housed under a fume hood, which allowed four mice to be simultaneously exposed to the aerosol. Air was drawn through the chamber at a rate of approximately 60 ml/minute and filtered through glass wool (Corning Inc., Corning, N.Y.) and charcoal traps (SKC Inc., Eighty Four, Pa.) upon exiting the exposure chamber. Each actuation of $\Delta^2$-THC or vehicle was delivered once per 5 s and the entire exposure period was 10 min. Mice were exposed to 20, 40 or 60 actuations of aerosolized $\Delta^2$-THC or 60 actuations of vehicle.

Mice were placed in separate clear chambers (16.5 cm×25.5 cm×11.5 cm high) and assessed for hypomotility using a Digiscan Animal Activity Monitor (Omni-tek Electronics Inc., Columbus, Ohio) in which the total number of
photocell-light beam interruptions was counted. Antinociception was assessed in the tail-flick test (D’Amour, F. E., Smith, D. L., A method for determining loss of pain sensation, J Pharm Exp Ther, 72:74–79 (1941)) with heat intensity adjusted to give baseline latencies ranging from 2.0–4.0 seconds. A cut-off time of 10 seconds was used to limit tissue damage. Percent maximum possible effect (%MPE) was determined according to the following formula:

\[
\text{%MPE} = \frac{\text{[test latency-baseline latency]/(cut-off-baseline latency)} \times 100
\]

A ring-test procedure was used to assess catalepsy. The percent of time during a five minute observation period that mice remained motionless, except for movements related to respiration, while stationed on a 5.7 cm diameter ring stand 23 cm above the laboratory bench, was assessed. Body temperature was assessed by inserting a thermometer probe (Traceable Digital, Control Co., Friendswood, Tex.) 2.5 cm into the rectum. Subjects were assessed for baseline tail-flick latency and rectal temperature prior to drug or vehicle administration. In the antagonism studies, mice were given an i.p. injection of SR 141716A or vehicle five-minutes prior to inhalation exposure of aerosols from 60 actuations of either a vehicle or a Δ^2-THC MDI. Locomotor activity, tail-flick latency, catalepsy, and hypothermia were assessed 5, 20, 40, and 60 minutes, respectively, after aerosol exposure. An additional group of animals was given an i.v. injection of Δ^2-THC (0.3, 1, 3, or 10 mg/kg) or vehicle into a lateral tail vein and assessed in the tail-flick test 20 minutes later. All injections were given in a volume of 0.1 ml per 10 g animal weight.

Blood and brain levels of Δ^2-THC were determined as follows. Extraction and LC-MS quantification of Δ^2-THC from whole blood and brain tissue were modified from Lichtman, A. H., Poklis, J. L., Wilson, D. M., Martin, B. R., The pharmacological activity of inhalation exposure to marijuana smoke in mice, Drug Alcohol Depend, 63:107–116 (2001). Particularly, THC and Δ^2-THC were extracted from brain material which contains a high degree of lipids. Acetone/nitrile was added to the pelletized solids and stored in a freezer overnight to separate the acetone/nitrile layer (which contained THC, Δ^2-THC) from the aqueous layers. The following day the acetone/nitrile layer was removed. In order to Lichtman et al., study, 2 ml of 9:1 NaOH was added and the sample was vortexed. Four mL of 9:1 hexane:ethyl acetate was added and the sample was vortexed and spun at 30 rpm for 30 minutes. The vials were then centrifuged at 4000 rpm at 30 rpm for 10 minutes. The organic layer was removed and evaporated. Upon drying, a derivatizing agent was added and the sample was vortexed, and each sample analyzed by GC/MS. In the present experimentation, the acetone/nitrile was instead evaporated to dryness under nitrogen. The material was then resublimed in 0.1 ml methanol. LC-MS identification was used to quantify Δ^2-THC/Δ^2-THC in blood and brain matrices. In the present experimentation, calibration standards were prepared from blank mouse whole blood and homogenized brain (2:1, water:brain, v:v). Fifty mg of Δ^2-THC (Radian Corporation, Austin, Tex.) was added to the blood sample, brain homogenate, and calibrators as an internal standard. Following an equilibration period, 2.5 ml of cold acetone/nitrile (HPLC grade, Fisher Scientific, Raleigh, N.C.) was added drop-wise while vortexing. The samples were then centrifuged (Precision Vari-Hi-Speed Centrifuge, Precision Scientific Co., Chicago, Ill.) at 2500 rpm for 15 minutes to pelletize solids, then stored in the freezer (−20°C) overnight, allowing the acetone/nitrile layer to separate from the aqueous layers. The acetone/nitrile layer was then removed and evaporated to dryness under nitrogen. The Δ^2-THC/Δ^2-THC was then resolubilized in 0.1 ml methanol (HPLC grade, Fisher Scientific).

LC-MS identification was used for quantification of Δ^2-THC and Δ^2-THC in blood and brain matrices using an 85:15 methanol: 1% glacial acetic acid (0.1% formic acid) mobile phase. A guard column was used inline with the standard reverse phase C18 column. The mass spectrometer was run in APCl+mode. Ions analyzed in single ion monitoring mode were 315 for Δ^2-THC and 318 for Δ^2-THC. A calibration curve was constructed for each assay based on linear regression using the peak-area ratios of Δ^2-THC to Δ^2-THC of the extracted calibration samples.

The statistical analysis of the data was as follows. Data are represented by means±standard error (s.e.). Statistical analysis of the data was performed using Student t-tests (for the physiochemical comparisons of the aerosol), or ANOVA (for pharmacological studies), with significance set at p<0.05. Post hoc tests for significant ANOVAs included either Dunnett’s test or Tukey/Kramer post-hoc analysis. All ED₅₀ values were determined using least squares linear regression analysis and calculation of 95% confidence limits (Bliss, C. L., Statistics in Biology (New York: McGraw-Hill, 1967) and were based on the number of actuations of the MDI (i.e., 1 mg/actuation). The Emax for depression of locomotor activity was calculated by double reciprocal plot. The Emax value for percent immobility was assigned the mean from the group that was exposed to 60 mg Δ^2-THC. The Emax values for antinociception and hypothermia were 100% MPE and 6° C. respectively. The ED₅₀ of SR 141716A in antagonizing the antinociceptive effects of Δ^2-THC was determined through least squares linear regression analysis and calculation of 95% confidence limits (Bliss, 1967). A sample size of 6–8 mice was used in each group.

Results: THC MDI Physiochemical Characteristics

As shown in Table 5 below, the physiochemical characteristics of the aerosolized Δ^2-THC were unaffected following storage at 40°C. with 82% relative humidity for 28 days. The mass of drug metered by the metering valve following a single actuation was reproducible and unaffected by the accelerated stability storage (p>0.1). There was little variance in the emitted dose and no significant effect of storage (p>0.1). The fine particle dose represented 23.0±0.8% before and 23.6±0.8% after accelerated stability testing of the emitted dose and exhibited no deterioration in Δ^2-THC content (p>0.1).

<table>
<thead>
<tr>
<th>TABLE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiochemical characteristics of the Δ^2-THC MDI</td>
</tr>
<tr>
<td>before and after accelerated stability testing (Mean ± s.e.c.)</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

Behavioral evaluation

Having thus determined that the tested MDI delivered a Δ^2-THC aerosol with particles of a sufficiently small mass for lung absorption, further experimentation was conducted to determine whether inhalation exposure to this aerosol could elicit systemic pharmacological effects in mice. Mice exposed to the Δ^2-THC aerosol exhibited cannabinoid activ-
ity in each of the four parameters tested (FIGS. 3A–D). Significant effects were found for locomotor inhibition (F(3, 28)=5.9, p<0.05) (FIG. 3A), antinociception (F(3,28)=7.8, p<0.05) (FIG. 3B), ring immobility (F(3,28)=10.0, p<0.05) (FIG. 3C), and hypothermia (F(3,28)=26.4, p<0.05) (FIG. 3D). The groups exposed to 40 and 60 actuations of Δ²-THC aerosol significantly differed from vehicle aerosol exposure (Dunnett’s test, p<0.05). ED₅₀ (95% CL) values were 32 (26–41) mg delivered for locomotor depression, 30 (20–44) mg delivered for antinociception, 32 (22–39) mg delivered for ring immobility, and 33 (25–44) mg of drug delivered for hypothermia.

FIGS. 4A–D show the effect of pretreatment with the specific CB₁ receptor antagonist, SR 141716A on the behavioral effects of inhaled Δ²-THC. Two-way ANOVA revealed that SR 141716A (10 mg/kg) significantly blocked Δ²-THC-induced hypomotility (F(1,28)=7.4, p<0.05), antinociception (F(1,28)=25.2, p<0.05), catalepsy (F(1,28)=7.4, p<0.05), and hypothermia (F(1,28)=28.9, p<0.05). The groups given a vehicle pretreatment and exposed to the Δ²-THC aerosol differed from all other groups for each measure (Tukey test, p<0.05).

The dose-response relationship of SR 141716A in antagonizing the antinociceptive effects following exposure to 60 mg of aerosolized Δ²-THC is shown in FIG. 5. SR 141716A significantly blocked the antinociception, F(5,30)=21.6, p<0.05, with an AD₅₀ (95% CL) of 0.8 (0.7–1.1 mg/kg).

Table 6 shows the blood and brain Δ²-THC concentrations, 20 mm after either inhalation exposure to Δ²-THC aerosol or intravenous injection of Δ²-THC. Increasing the amount of drug delivered resulted in increasing concentrations of Δ²-THC in both matrices. The blood levels of Δ²-THC following aerosol exposure 20, 40, or 60 mg delivered increased in a dose dependent fashion and were comparable to the blood levels produced by intravenous injection of 3 and 10 mg/kg Δ²-THC. Brain levels of Δ²-THC following those exposures were similar to that of 1 and 3 mg/kg intravenous injection of Δ²-THC. There was dissociation in Δ²-THC blood and brain concentrations between the inhalation and intravenous routes of administration, an interesting result because other drugs such as methamphetamine, heroin and phencyclidine have been observed to lead to similar brain-blood plasma ratios between the two routes of administration. For the present experimentation, whereas brain levels were 200–300% higher than blood levels following i.v. injection of Δ²-THC, the brain levels of Δ²-THC were roughly equivalent to the blood levels of Δ²-THC following inhalation.

**TABLE 7**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Blood ED₅₀ (95% CL)</th>
<th>Brain ED₅₀ (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>591 (483–806)*</td>
<td>506 (333–769)*</td>
</tr>
<tr>
<td>Intravenous</td>
<td>2.4 (1.4–4.2) mg/kg</td>
<td>230 (102–521)</td>
</tr>
</tbody>
</table>

*Potency ratios (95% CL) in blood, 1.8 (0.5–4.2), and in brain, 0.6 (0.2–1.5), were not significantly different.

The HFA 134a-ethanol formulated MDI delivered a respi rable Δ²-THC aerosol in an accurate and reproducible fashion. Preliminary accelerated stability testing revealed that no significant degradation of the Δ²-THC occurred following storage in extreme conditions. Mice exposed to the aerosol exhibited a full spectrum of pharmacological effects indicative of cannabinoid activity (Compton et al., 1993; Little, P. J., Compton, D. R., Johnson, M. R., Melvin, L. S., Martin, B. R., Pharmacology and stereoselectivity of structurally novel cannabinoids in mice, J Pharmacol Exp Ther, 247:1046–1051 (1988)) including hypotension, antinociception, catalepsy, and hypothermia. Each of these responses was dose-dependent and antagonized by SR 141716A, indicating a CB₁ receptor mechanism of action. The hypothermic effects of Δ²-THC were not completely antagonized. SR141716A’s low ED₅₀ (i.e., 0.8 mg/kg) in antagonizing the antinociceptive effects of inhaled Δ²-THC is in agreement with those of previous reports including exposure to marijuana smoke (0.6 mg/kg; Lichtman et al., 2001), injection of Δ⁹-THC (0.4 mg/kg; Compton, D., Aceto, M., Lowe, J., Martin, B., In vivo characterization of a specific cannabinoid receptor antagonist (SR141716A): inhibition of delta-9-tetrahydrocannabinol-induced responses and apparent agonist activity, J Pharmacol Exper Ther, 277, 586–594 (1996)), or injection of the synthetic cannabinoid WIN 55,212-2 (1.6 mg/kg; Rinaldi-Carmona, M., Barth, E., Heaume, M., Shire, D., Calandra, B., Congy, C., Martinez, S., Maruani, J., Nellat, G., Caput, D., Ferrara, P., Sotiriou, P., Brelie, J. C., Le Fur, G., SR141716A, a potent and selective antagonist of the brain cannabinoid receptor, FEBS Lett, 350:240-244 (1994)).

**Antinociceptive effect and blood and brain concentrations of Δ²-THC 20 min after treatment**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>THC dose</th>
<th>% MPE (mean ± S.E.)</th>
<th>ng Δ²-THC/g blood (mean ± S.E.)</th>
<th>ng Δ²-THC/g brain (mean ± S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>20 actuations</td>
<td>37 ± 11*</td>
<td>409 ± 86</td>
<td>340 ± 36</td>
</tr>
<tr>
<td></td>
<td>40 actuations</td>
<td>58 ± 14*</td>
<td>788 ± 273</td>
<td>791 ± 64</td>
</tr>
<tr>
<td></td>
<td>60 actuations</td>
<td>78 ± 11*</td>
<td>1152 ± 240</td>
<td>890 ± 151</td>
</tr>
<tr>
<td>Intravenous</td>
<td>1 mg/kg</td>
<td>31 ± 8</td>
<td>102 ± 6</td>
<td>307 ± 28</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg</td>
<td>70 ± 14</td>
<td>365 ± 39</td>
<td>854 ± 42</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg</td>
<td>67 ± 11</td>
<td>1324 ± 38</td>
<td>3307 ± 190</td>
</tr>
</tbody>
</table>

*From FIG. 3B

Comparison of MDI antinociceptive potency with blood and brain concentrations of Δ⁹-THC resulted in a high correlation (r²=0.997 and r²=0.889 for blood and brain, respectively). Additionally, comparison of blood and brain levels of Δ⁹-THC at antinociceptive EC₅₀ doses for inhalation and i.v. injection of Δ⁹-THC as well as comparison of potency ratios between the two routes of administration revealed no significant differences in the different matrices (Table 7).

Unlike parenteral methods of delivery in which a known amount of drug is injected, determining the absorbed dose of an inhaled drug is difficult to quantify. Although a large mass of drug was actuated into the inhalation chamber, the major-
ity of drug mass is lost because it either deposits on the exposure apparatus or escapes with exhausted air out of the apparatus. Additionally, physiological properties, such as tidal volume and respiratory rate, influence drug inhalation. Finally, because mice are obligate nasal breathers, many particles do not reach the lungs. Therefore, for the above experiment, dose was indirectly assessed by comparing the concentration of Δ⁹-THC in whole blood and brain after inhalation and i.v. routes of administration. For both routes of administration, the concentrations of drug increased in both matrices with increasing doses. Inhalation exposure of each respective dose of aerosolized Δ⁹-THC resulted in equivalent concentrations of the parent compound in blood and brain. On the other hand, i.v. administration resulted in Δ⁹-THC brain levels that were approximately two to three fold higher than those found in blood. The EC₅₀ values for inhalation exposure and i.v. injection in the above experiment were not significantly different in either matrix. Consequently, exposure to the Δ⁹-THC aerosol produced dose-dependent increases of Δ⁹-THC in blood and brain levels, and the levels necessary to produce cannabinoïd behavioral effects were similar to i.v. injection.

In the above results of the above experiment on mice to other animals, it will be taken into account that mice are obligate nose-breathers with an extensive nasal infra-architecture, such that substantial nasal deposition may have hindered alveoli deposition. Schlesinger (1985) reported upper respiratory tract deposition of particle sizes between 2-3 μm ranged from 20-40%. Schlesinger, R. B., Comparative deposition of inhaled aerosols in experimental animals and humans: a review, J Toxicol Environ Health, 15:197–214 (1985). Using empirical modeling, Asgharian et al. (1995) calculated that less than 15% of particles with a mass median aerodynamic diameter of 2-3 μm could reach the alveolar regions of rats compared to a 40% value in humans, and this percentage would be expected to be even lower in mice because of the smaller respiratory tract and general anatomical differences between rats and mice. Asgharian, B., Wood, R., Schlesinger, R. B., Empirical modeling of particle deposition in the alveolar region of the lungs: A basis for interspecies extrapolation, Fund Appl Toxicol, 27, 232–238 (1995). Consequently, a considerable amount of the exposed dose is likely to have been deposited in the upper respiratory tract of the mice. In addition, any impacted particles could be moved to the throat, via ciliary action, and swallowed, resulting in gastrointestinal absorption. However, such absorption would not be expected to be as rapid as alveolar absorption. Hence, this delayed absorption might act to maintain Δ⁹-THC blood and brain levels for a prolonged period of time. Despite the extensive filtering done by mice, the fine particle dose generated by the MDI (i.e., 0.22 mg per actuation) was sufficient to result in the rapid elicitation of pharmacological behavior suggesting that the behavioral effects were due to absorption in either the lungs or the upper respiratory tract and not due to gastrointestinal absorption. Nonetheless, nasal filtering is of little concern in humans and the fact that locomotor depression occurred within 5 minutes of exposure and antinociception occurred at 20 minutes is consistent with the notion that a sufficient amount of the aerosol reached the lungs.

The results of Tables 5–7 and FIGS. 3A–5 show, inter alia, that a Δ⁹-THC MDI was formulated that can be used to provide a systemic dose of Δ⁹-THC via the lungs, and that a Δ⁹ THC MDI is capable of producing the full constellation of cannabinoid effects in mice. Physiochemical characteristics of the aerosol were assessed before and after accelerated stability testing. Following this characterization, mice were exposed to the aerosol and evaluated for pharmacological effects indicative of cannabinoid activity, including hypomotility, antinociception, catalepsy, and hypothermia. The CB₁ receptor antagonist SR 141716A was used to determine whether the pharmacological effects were mediated by the cannabinoid receptor. The fine particle dose of Δ⁹ THC was 0.22±0.03 mg (mean±S.D.) or 25% of the emitted dose. In addition, the physiochemical properties of the aerosol were unaffected by accelerated stability testing. A 10-minute exposure to aerosolized Δ⁹ THC elicited

### TABLE 8

<table>
<thead>
<tr>
<th>Administration</th>
<th>Δ⁹-THC blood level (ng Δ⁹-THC/ml blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebulized aerosol*</td>
<td>100</td>
</tr>
<tr>
<td>MDI aerosol** (20 actuations)</td>
<td>400</td>
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</tbody>
</table>

*Emulphor as the surfactant  
**Ethanol cosolvent; HFA 134a propellant

Other advantages of Δ⁹-THC delivery according to the present invention also are seen. The present invention delivers a systemic dose of Δ⁹-THC via the lungs. The development of a Δ⁹-THC MDI, which leads to a rapid onset of action, consistent blood levels, and by-passing the first-pass metabolism in the liver, suggests the viability of the Δ⁹-THC aerosol as a replacement for oral Δ⁹-THC.

In sum, the experimentation discussed above with regard to Tables 5–7 and FIGS. 3A–5 show, inter alia, that a Δ⁹-THC MDI was formulated that can be used to provide a systemic dose of Δ⁹-THC via the lungs, and that a Δ⁹ THC MDI is capable of producing the full constellation of cannabinoid effects in mice. Physiochemical characteristics of the aerosol were assessed before and after accelerated stability testing. Following this characterization, mice were exposed to the aerosol and evaluated for pharmacological effects indicative of cannabinoid activity, including hypomotility, antinociception, catalepsy, and hypothermia. The CB₁ receptor antagonist SR 141716A was used to determine whether the pharmacological effects were mediated by the cannabinoid receptor. The fine particle dose of Δ⁹ THC was 0.22±0.03 mg (mean±S.D.) or 25% of the emitted dose. In addition, the physiochemical properties of the aerosol were unaffected by accelerated stability testing. A 10-minute exposure to aerosolized Δ⁹ THC elicited
hypomotility, antinociception, catalepsy, and hypothermia. Additionally, $\Delta^8$ THC concentrations in blood and brain at the antinociceptive ED$_{50}$ dose were similar for both inhalation and intravenous routes of administration. Finally, pretreatment with 10 mg/kg (i.p.) of SR 141716A significantly antagonized all of the $\Delta^8$ THC-induced effects. These results indicate that an MDI is a viable method to deliver a systemic dose of $\Delta^8$ THC that elicits a full spectrum of cannabinoid pharmacological effects in mice that is mediated via a CB$_1$ receptor mechanism of action.

The experimental findings set forth herein suggest that an aerosolized form of $\Delta^8$ THC for medicinal use may be provided. Dosages for mice have been provided, and typically human doses are about 100 times lower than mouse doses on a mg/kg basis. The demonstration that a $\Delta^8$-THC aerosol, generated by an MDI, is relatively stable and produces systemic pharmacological effects in mice has clinical applications in the treatment of many disorders, including pain management as well as the indications for orally available $\Delta^8$-THC. The availability of a highly reproducible $\Delta^8$-THC aerosol, without exposure to potentially harmful chemicals and carcinogens present in marijuana smoke, is particularly advantageous for the treatment of human patients.

While in the present invention use of $\Delta^8$ THC (see FIG. 7A) is particularly preferred, it will be appreciated that in place of $\Delta^8$ THC may be used $\Delta^8$-THC derivatives and substitutives, e.g., $\Delta^8$ THC (FIG. 7B), 11 hydroxy $\Delta^8$-THC (FIG. 7C), cannabiol (CBN) (FIG. 7D), cannabidiol (CBD) (FIG. 7E); synthetic cannabinoids such as nabilone (FIG. 7F), levonantradol (FIG. 7G), (-)-HU-210 (FIG. 7H); Win 55212-2 (FIG. 7I); Anandamide (FIG. 7J); Methandamine (FIG. 7K); CP 55940 (FIG. 7L); 1-O-1057 (FIG. 7M); SR141716A (FIG. 7N).

While the invention has been described in terms of its preferred embodiments, those skilled in the art will recognize that the invention can be practiced with modification within the spirit and scope of the appended claims.

We claim:

1. A method of administering a pharmaceutically effective dose of aerosolized $\Delta^8$ tetrahydrocannabinol to a patient, comprising the steps of:
   - providing a solution comprising a pharmaceutically acceptable form of $\Delta^8$ tetrahydrocannabinol (THC) in a hydrofluoralkane, said solution having not more than 15% w/w of a pharmaceutically acceptable solvent;
   - aerosolizing the THC solution to provide respirable droplets comprising THC wherein at least 20% of the mass of the respirable droplets comprise droplets having an aerodynamic diameter of less than 5.8 $\mu$m;
   - administering a pharmaceutically effective dose of said respirable droplets to a patient’s lungs.

2. A method of administering a pharmaceutically effective dose of aerosolized $\Delta^8$ tetrahydrocannabinol to a patient, comprising the steps of:
   - providing a solution comprising a pharmaceutically acceptable form of tetrahydrocannabinol (THC) in a hydrofluoralkane, said solution having not more than 15% w/w of a pharmaceutically acceptable solvent;
   - aerosolizing the solution to provide respirable droplets comprising THC wherein at least 20% of the mass of the respirable droplets comprise droplets having an aerodynamic diameter of less than 5.8 $\mu$m;
   - administering a pharmaceutically effective dose of said respirable droplets to a patient’s lungs.

3. The method of claim 2 wherein said solution comprises less than 15% w/w of a solvent selected from the group consisting of ethanol, propanol, propylene glycol, glycerol, and polyethylene glycol.

4. The method of claim 3 wherein said solvent comprises ethanol.

5. The method of claim 1 wherein said solution consists essentially of a hydrofluoralkane propellant and $\Delta^8$-tetrahydrocannabinol.

6. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to reduce nausea.

7. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to reduce vomiting.

8. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to reduce pain.

9. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to relieve muscle spasticity.

10. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to relieve migraine headaches.

11. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to relieve movement disorders.

12. The method of claim 1 wherein said pharmaceutically effective dose is sufficient to increase appetite in patients suffering from cachexia.

13. The method of claim 2 wherein said pharmaceutically acceptable form of THC is pure $\Delta^8$-tetrahydrocannabinol and said hydrocarbon is selected from the group consisting of hydrofluoralkane (HFA) 134a and HFA 227.

14. The method of claim 2 wherein the droplets are less than about 10 $\mu$m.

15. A method according to claim 1 wherein the pharmaceutically effective dose is effective to achieve a serum concentration level in a patient of 10–100 ng/ml fifteen minutes following inhalation.

16. A method according to claim 1 comprising a pharmaceutically acceptable salt of $\Delta^8$-tetrahydrocannabinol.